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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,655	PADUA ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-26, and 39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-26 and 39-44* is/are rejected.

7)☒ Claim(s) *41 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' submission of a corrected list of claims on 03/03/2005 is acknowledged.

Claims 5, 6, and 27-38 are cancelled (see the interview summary of 11/10/2005 for details). Claims 1-4, 7-26, and 39-44 are pending.

Note: Change in Art Unit and SPE

The examiner has been reassign to Art Unit 1633. Therefore, future correspondence should reflect such changes. The information regarding the SPE and Art Unit is at the end of the Action.

Specification

Claims 41 and 44 are objected to under 37 CFR 1.75(c), as being improper of improper dependent form for failing to further limit the subject matter of the previous claims, 1, 39 and 40. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 41 and 44 are drawn to a genetically engineered cell, while claims 1, 39, and 40 are drawn to a therapeutic delivery system comprising an electrical pulse generator operably linked to a genetically engineered cell. Since claims 41 and 44, drawn to a the genetically engineered cell, do not recite the electrical pulse generator of claims 1, 39, and 40, claim 44 does not further limit claims 1, 39, and 40.

Claim Rejections - 35 USC § 112 – enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4, 7-26, and 39-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) electrically stimulated induction of gene expression *in vitro* using an electrical pulse generator operably coupled with cultured genetically engineered cells comprising a target gene operably coupled to an electrically responsive promoter and (ii) delivering to a subject an electrical pulse generator operably coupled to genetically engineered cells, wherein genetically engineered cells are transplanted into the ssubject, does not reasonably provide enablement for (i) a therapeutic delivery system comprising an electrical pulse generator operably coupled with genetically engineered cells in a mammalian tissue, wherein said genetically engineered cells further comprise a target gene operably coupled to an electrically responsive promoter and (ii) a method of treating a patient comprising providing the patient with an electrical pulse generator operably coupled with genetically engineered cells in a patient tissue, wherein said genetically engineered cells further comprise a target gene operably coupled to an electrically responsive promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. While determining whether a specification is enabling, one

considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The instant claims 1-4, 7-26 are drawn to a therapeutic delivery system comprising electrically stimulated delivery of therapeutic products from cells that have been genetically engineered to express an electrically responsive promoter operably coupled to the genes encoding for the therapeutic products.

Such language directed to a therapeutic delivery system is considered to directly embrace administering to animals a therapeutic agent in an amount sufficient such that the treatment of an animal having a condition associated with the therapeutic agent is achieved. Accordingly, preamble language directed to "therapeutic delivery system" is considered to require support as outlined in 35 U.S.C. § 112 first paragraph such that therapeutic benefit is considered to be enabled for one seeking to make and use such a delivery system.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The Breadth of the Claims

The instant claims 1-4, 7-26 are drawn to a therapeutic delivery system comprising an electrical pulse generator operably coupled with genetically engineered cells in a mammalian tissue, wherein said genetically engineered cells further comprise a target gene operably coupled to an electrically responsive promoter. The instant claims 39-43 are drawn to a method of treating a patient using the above-mentioned therapeutic delivery system.

The aspects considered broad are: (i) the range of diseases to be treated, (ii) the range of target gene that can be used as therapeutic agents, and (iii) the range of genetically modified cells. As will be shown below, these broad aspects are not enabled.

The Nature of the Invention

The nature of the invention is the use of an electrical pulse generator to drive the expression of therapeutic agents to treat various diseases. Such invention has use in the art for treating various forms of disorders.

However, the nature of such invention is within the broad genera of disorders treatment and disorders treatment does not generally enable Applicants' invention due to problems with the complexity and unpredictability of such disorders and also due to

problems with using nucleic acid-based therapies, i.e., efficient and cell-specific delivery.

The broad term disease encompasses distinct diseases that are caused by different genetic factors and result in different clinical manifestation. For example, the neurodegenerative disorders are caused by mutations of distinct genes that affect different areas of the brain, for example presenilin and amyloid precursor proteins (Alzheimers' disease), α-synuclein (Parkinson's disease), superoxide dismutase (amyotrophic lateral sclerosis or Lou Gehrig's disease), huntingtin (Huntington's disease) are the cause of distinct neurodegenerative diseases with distinct clinical manifestations (Hardy et al., Review, Science, 1998, 282: 1075-1079). Also they could result in a similar symptom. How will therapeutic apply in these cases? The Artisan would not know what therapeutic agent to use to treat a symptom that can be caused by mutations in a number of different genes. With respect to this complexity and unpredictability of neurodegenerative diseases Hardy et al. teach:

> "[T]he phenotype of a given mutation may not clearly predict a single expected clinicopathological entity. In the ataxias, abnormalities occur in any of a number of different genes, yet the clinical syndromes from the varied mutations are strikingly similar to each other.
>
> A key issue in the current research in neurodegenerative disease is that of select vulnerability.
>
> Only by considering this selectivity can we compare and contrast the biological mechanism of the disease. Each strikes a seemingly select group of neurons. Huntington's disease causes cell death in the caudate and results in chaotic movement. Parkinson's disease destroys cells in substantia nigra, resulting in rigidity and tremor and preventing initiation of movement. Amyotrophic lateral sclerosis damages the lower motor and pyramidal neurons and causes weakness and spacicity. Alzheimer's disease isolates the hippocampus and parietal lobes and prevents formation of new memory."

Moreover, many diseases arising from injury or genetic abnormalities require one or more pharmacological agents for treatment. There are a growing number of polygenic diseases, such as hypertension, renal disease. How will therapeutic apply to polygenic diseases? The use of single drugs or single genes may often not work very well, due to the complexity of regulatory pathways. Tresco et al. (Advanced Drug Delivery Reviews, 2000, 42: 3-27) teach:

> "Although progress has been made in understanding the etiology and pathogenesis of diseases, in developing animal models and newer experimental therapeutics, few discoveries have been translated into clinically effective ways of delivering the multiple therapeutic agents obtained from living mammalian cells.
>
> Gene therapy, be it *in vivo* or *ex vivo,* so far has mostly been applied to monogenic diseases or in the lack of solid genetic evidence, diseases in which a single soluble compound is missing. Clearly, many more diseases are multifactorial in nature and consequently more difficult to treat. Furthermore, not all diseases are the result of missing soluble factors. The kinds of technical issues posed by more complicated diseases certainly have yet to be addressed. But gene therapy is a relatively new field that has only recently entered the clinical realm, and many fundamental issues still need to be addressed in the various disciplines that genetic engineering encompasses."

Given these teachings, one skilled in the art would not know what gene to use to treat a clinical syndrome caused by mutations in a number of different genes, what genes to use to treat multifactorial diseases, or how to specifically deliver the therapeutic gene to the affected cells, without altering the non-affected cells.

With respect to nucleic acid-based therapies, Applicants disclose that the therapeutic gene may be introduced into the target tissue as part of an expression vector in a pharmaceutically acceptable carrier, either by direct administration to the tissue or by systemic delivery. Meyer et al. (Review, Cell. Mol. Biol., 2001, 47: 1277-1294) teach:

> "Although gene therapy provides the hope and potential to revolutionize the future of medicine, this optimism must be tempered. Ongoing efforts to both quantitatively increase both gene transfer and expression to achieve improved therapeutic effect and to restrict the distribution and expression to relevant target tissues are under development. This includes enhancing the permeation of the vectors, development of targeted vectors that can be delivered systematically and regulating the level and target cell specificity of gene expression. Although these technologies are under development, advances in these areas will further improve the efficacy and safety of gene therapy vectors and further increase chances of success."

Hence, from the nature of the invention, the Artisan would not reasonably predict that the delivery system claimed by the instant application could be used to treat diseases in general.

The State of the Prior Art and the Level of Predictability in the Art

At the time the invention was made, and even in the present, the art of treating disorders was known to be unpredictable with respect to efficacy of delivering the nucleic acids to the targeted cells or tissues and a prolong expression of the therapeutic gene of interest.

The problems of nucleic acids based therapies are well known in the art, particularly with regard to the delivery systems, the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is expressed to a degree necessary to result in a therapeutic effect.

For example, with respect to specific delivery and gene expression, Fisher A. (Review, Cell. Mol. Biol., 2001, 47: 1269-1275) teaches:

> "In spite of its logic, this therapeutic approach is complex considering the manner in which one must search in order to obtain a prolong expression of the therapeutic protein of interest. This objective contains several barriers: the difficulty in many cases of targeting cells (for example, the epithelial cells of the respiratory tract or of muscular fibers), the life duration of these cells, and the loss of expression of the transgene which is linked to several factors.

> For ten years, about 500 clinical gene therapy trials have been undertaken globally, with 80% of them occurring in the United States. Despite the fact that many of these experiments are more interested in issues of tolerance and pharmacology (phase I/II) that in efficacy, only very few have provided any proof of efficacy as of yet. Actually, this is easily explained by the difficulties of this therapeutic approach: it is necessary to obtain the expression of a potentially therapeutic gene that requires a good understanding of the disease's physiopathology in the targeted cells, at a level that is neither too low (efficacy) nor too high (toxicity). Ten years of clinical trials tests is not very much! It is true, however, that many actors in the research have largely underestimated the encountered difficulties."

With respect to the problems encountered with the delivery systems, Gardlik et al. (Review, Med. Sci. Monit., 2005, 11: RA110-121) teach:

> "The simplest way of gene delivery is injecting naked DNA encoding the therapeutic protein, but because of low efficiency there is a need to use special molecules and methods to improve gene delivery.
>
> Two kinds of vectors have been employed as vehicles for gene transfer. Viral vectors for gene transduction, such as retroviral, adenoviral, and adeno-associated viral vectors, and non-viral vectors for gene transfection, such as plasmids and liposomes. However, each vector has its own advantages and disadvantages: none of these types of vectors has been found to be ideal for both safe and efficient gene transfer and stable and sufficient gene expression"

Therefore, at the time the instant invention was made, the therapeutic use of nucleic acids to treat disorders in general was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) in general. Such obstacles include, for example, problems with delivery, target accessibility and stable and sufficient protein expression in the desired cells. For example, Lowenstein et al. (Review, Current Opinion in Pharmacology, 2004, 4: 91-97) teach:

> "Could vectors, transgenes or transgenic proteins access the brain from the circulation? Delivery of viral vectors into the brain through a systemic route would be of great importance, but has so far neither been achieved nor explored in detail. Clearly this

would be attractive because of the large areas of the brain that are affected in human neurodegenerative diseases."

In his review article, Tuszynski (Expert Opin. Biol. Ther., 2003, 3: 815-828) teaches:

"[T]here are also some relative potential disadvantages of *in vivo* gene therapy, including:

Non-specificty of target cell infection – many different cell types can be infected when *in vivo* vectors are injected into CNS, including neurons, glia and vascular cells. Overexpression of therapeutic genes such as nervous system growth factors in neurons could hypothetically exert deleterious effects by bypassing normal cell surface receptors binding mechanisms for growth factors.

Thus, the potential of gene therapy to treat disease of the nervous system is vast and unprecedented, yet entirely hypothetical at this early stage of development."

Given these teachings, the skilled artisan would not know *a priori* whether introduction of the expression vector *in vivo* by the broadly disclosed methodologies of the instant invention, would result in expression vector reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful therapy. One of skill in the art would not know how to deliver nucleic acids to an organism in such a way that would ensure an amount sufficient to stably and sufficiently express the therapeutic gene in the proper cell.

Applicants also contemplate to administer therapeutic products by the transplantation of genetically engineered cells in conjunction with electro-stimulation. Tresco et al. teach:

"[T]ransplanted cells must be considered as a viable alternative to conventional delivery systems.
Available information from studies conducted thus far have identified a number of critical questions that must be addressed in order for this promising approach to make transition from a boutique laboratory to a common component of the medical armamentarium".

Some of the questions to be addressed are: should the therapeutic agent be produced constitutively or should it be released in a regulated manner, what type of cell is optimal as a delivery vehicle, is the therapeutic effect to be achieved over short-time or over a more prolonged interval, should the transplanted cells be allowed to integrate into host tissue, or are they to be maintained physically isolated, do transplanted cells have the potential to migrate away from the site of transplantation?

With respect to the above questions, Tresco et al. teach that (i) many diseases, such as enzymatic deficiency disorders, do not require regulated delivery; in contrast, in certain situations, such as diabetes, regulated delivery is critical (p. 4, column 2, fourth paragraph); (ii) choosing the optimal type of cell is very important, depending on the desired outcome: cell phenotype, or biosynthetic activity of the cell or the turnover rate *in vivo* each has to be considered for optimal results (p. 5, column 1, second paragraph), (iii) the inherent turnover of the cell type delivered is the key difference between short-term or long-term treatments; for genetically modified cells the efficacy of the original genetic modification is critical. The inactivation of the transgenes is an important obstacle for the treatment of chronic disorders by gene therapy (p. 5, column 1, third paragraph), (iv) if it is not possible to transplant autologous cells, cell encapsulation might be required to protect the donor cells from destruction by the immune system (p. 5, column 1, last paragraph), and (v) the migratory capacity of the cell used as a delivery vehicle must be considered; for systemic delivery of agents one

desires to have cells migrate, for local delivery one desires to have cells remain at a specific site (p. 5, column 2, second paragraph).

Given these teachings, the skilled artisan would not know *a priori* whether introduction of any genetically modified cell *in vivo* by the broadly disclosed methodologies of the instant invention, would result in therapeutic agent reaching the proper target in a sufficient concentration and remaining for a sufficient time to provide successful therapy. One of skill in the art would not know what type of genetically modified cell to deliver to an organism in such a way that would ensure an amount sufficient to stably and sufficiently express the therapeutic gene at the proper site, to treat diseases in general.

While the intent is not to say that nucleic acids or genetically modified cell transplants can never be used to treat diseases, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given this unpredictability, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the claimed methods *in vivo* in an enormous number of organisms as broadly or generically claimed, with a resultant treatment of diseases in general, as claimed.

In fact, the state of the art is such that successful delivery of nucleic acids *in vivo* or *in vitro*, such that they provide the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of gene therapy using nucleic acids in general *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate

cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, treatment of diseases in general.

Similarly, the state of the art for successful delivery of therapeutic agents via genetically modified cell implants to provide the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of gene therapy using genetically modified cell implants are unpredictable with respect to delivery of the therapeutic molecule such that the therapeutic molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the therapeutic molecule is effective in, as in the instant application, treatment of diseases in general.

The Amount of Direction or Guidance/The Existence of Working Examples

The specification does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of using nucleic acids or genetically modified cell implants in therapeutic applications in any organism. The field of nucleic acids/genetically modified cell implants therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

It is noted that specification discloses one *in vitro* example for using electrical pulse to stimulate the expression of the luciferase gene in cultures of genetically engineered cells comprising the luciferase gene under the control of the ANF promoter. It is also noted that the specification discloses one example of electrical stimulation of

dogs that received a transplant of cultured skeletal myoblasts after experimentally induced myocardial infarction. However, the myoblasts used for transplantation were not genetically modified, i.e., did not comprise a construct composed of a target gene operably linked to an electrically-responsive promoter, therefore the limitation recited in the instant claims is not met.

Given the diverse and unpredictable outcome of using the disclosed delivery system to treat diseases, the specification does not appear to provide sufficient guidance and/or working examples that specifically address the use of this delivery system as being effective in treating various diseases in animals to enable one of ordinary skill in the art to use such delivery system without undue experimentation.

Gilmour et al. (Developmental Biology, 1995, 168, 416-428) teach:

> "Data presented here indicate that the enhancer activity of this region of the γ subunit gene seen in Sol8 muscle cells and MyoD-cotransfected 10T1/2 fibroblasts does not exist in rat primary muscle cultures.....indicating physiological differences between the established Sol8 cell line and primary muscle culture. The data presented here indicate that, although analysis of transcriptional activity in immortalized cell lines is a valuable tool due to the homogeneity of the cultures and ease of preparation, further analysis in primary cell cultures (or animal models) is necessary in order to draw more valid conclusions as to the relevance of experimental results to transcriptional mechanisms in *vivo*".

Conclusion

In conclusion, the presently claimed invention only provides enough of a disclosure to allow for an Artisan to: (i) electrically stimulate induction of gene expression *in vitro* using an electrical pulse generator operably coupled with cultured genetically engineered cells comprising a target gene operably coupled to an electrically responsive promoter (claims 1-4 and 7-26), and (ii) delivering to a subject an electrical

pulse generator operably coupled to genetically engineered cells, wherein genetically engineered cells are transplanted into the subject (claims 39-43).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4, 11, 23, 24, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Gilmour et al. (Developmental Biology, 1995, 168, 416-428).

Gilmour et al. teach electrical pulse stimulation of primary muscle cells transfected with luciferase operably coupled to the nicotinic acethylcholine receptor γ subunit promoter (p. 418, column 2, Transfection and Electrical Stimulation). Gilmour et al. teach that the nicotinic acethylcholine receptor γ subunit promoter mediates suppression of transcription in response to electrical activity (p. 421, column 1, last paragraph, column 2, first paragraph, p. 423, Fig. 4, and p. 424, column 2, Discussion). The pulses do not appear to damage the cells and thus, are considered to be subtheshold-applied pulses.

Since the art teaches electrically stimulation of gene expression *in vitro* using an electrical pulse generator operably coupled with cultured genetically engineered cells

comprising a target gene operably coupled to an electrically responsive promoter, the claimed inventions are anticipated by the above-cited art.

7. Claims 1-4, 11, 13, 23, 24, and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Yanagida et al. (Journal of Biotechnology, April 14, 2000, 79: 53-61).

Yanagida et al. teach 3T3 cells transfected with luciferase operably coupled to the hsp70 promoter (p. 56, column 2, last paragraph). Yanagida et al. teach that electrical pulse stimulation of the hsp70 promoter results in induction of luciferase expression (p. 55, column 2 and p. 58, Fig. 5). The pulses do not appear to damage the cells and thus, are considered to be subtheshold-applied pulses.

Since the art teaches electrically stimulation of gene expression *in vitro* using an electrical pulse generator operably coupled with cultured genetically engineered cells comprising a target gene operably coupled hsp70 promoter, the claimed inventions are anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-4, 7- 11, 13, 14, 23-25, and 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Circulation, Aug, 22, 2000, 102: 898-901), in view of Kanno et al. (Circulation, 1999, 99: 1682-1687).

Lee et al. teach implantation of primary murine myoblasts expressing the murine VEGF gene from a retroviral promoter into the ventricular wall of immunodefficient mice (Abstract, p. 899, column 1, Materials and Methods). Lee et al. do not teach an electrically responsive promoter or induction of VEGF by electrical stimulation. Kanno et al. teach induction of VEGF in electrical pulse stimulated murine myoblast cell line C2C12 (p. 1682, column 2, Methods, and p.2684, column 2, second and third paragraphs). Kanno et al. do not teach implantation of myoblasts. Kanno et al. that their procedure could be used in therapeutic angiogenesis, for example in ischemic diseases (Abstract, p. 2686, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Lee et al. to transplant genetically engineered myoblasts expressing VEGF and increase VEGF expression by generating an electrical pulse, as taught by Kanno et al., with a reasonable expectation of success. The motivation to do so is provided by Kanno et al. who teach gene therapy as relevant for therapeutic angiogenesis and the importance of transplanting VEGF-expressing cells in the ischemic area only since localized, controlled expression of VEGF induced by electrical pulse stimulation, thereby inducing the activity of the promoter which would activate local VEGF production, salvaging the ischemic area (Abstract, and p. 2686, column 2, last paragraph) and by Lee et al. who teach potential toxicity of unregulated myoblasts-mediated VEGF expression (p. 900,

column 2, last paragraph). Thus, the claimed invention was prima facie obvious at the time the invention was made.

10. Claims 1, 7-10 are rejected under 35 USC 103(a) as being unpatentable over either Gilmour et al. or Yanagida et al., as applied to claim 1, and further in view US 20010031919 A1.

Either Gilmour et al. or Yanagida et al., does not teach explicitly the limitations of using a pacemaker or any electrical device implanted or externally controlled so as to provide an electrical pulse for gene expression in desired cells.

However, at the time the invention was made, the 20010031919 A1 reference did teach that a pace maker can be attached to a gene delivery tool (claim 22, par. 0136). Thus, it would have been obvious for one of ordinary skill in the art to employ any know device for providing an desired amount of pulses as taught by the primary reference, e.g., Gilmour et al. or Yanagida et al.

One of ordinary skill in the art would have been motivated to employ a pulse making device such as a pace maker implanted internally or externally because such devices are well known in the art and the use of the device would provide the sources of pulses as required for providing a stimulation of gene expression, which electrical pulse stimulation of a promoter is crucial for modulation of gene expression as taught by the primary reference. One of ordinary skill in the art would have a reasonable expectation of success in making and use such as the combined composition because medical

devices such as pace makers are proven to provide any amount of pulses as desired in stimulating gene expression.

Thus, the claimed invention was prima facie obvious at the time the invention was made.

11. Claims 1, 12, 14, and 16-22 are rejected under 35 USC 103(a) as being unpatentable over Gilmour et al., as applied to claim 1, in view of Allen (Ann Thorac Surg, 1999, 68: 1924-1925).

Gilmore et al. do not teach the limitation of using a tissue specific promoter. However, at the time the invention was made, Allen did teach organ-selective local delivery of therapeutic genes (Abstract, page 1924 bridging page 1925, column 1, first paragraph). Thus, it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to genetically alter cells with a construct comprising the electrically responsive enhancer of Gilmour et al. and link it to a tissue specific promoter for local delivery, as taught by Allen, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to employ such a chimeric enhancer-promoter construct in conjunction with an electrical pulse generator for controlled delivery of genes to specific organs/tissue, since the electrical pulse stimulation of a promoter is crucial for modulation of gene expression as taught by the primary reference. One of ordinary skill in the art would have a reasonable expectation of success in making and use such as the combined composition because electrically

responsive enhancers are proven to promote gene expression as desired, upon electrical stimulation.

Thus, the claimed invention was prima facie obvious at the time the invention was made.

12. Claims 1 and 15 are rejected under 35 USC 103(a) as being unpatentable over Gilmour et al., as applied to claim 1, in view of McDonough et al. (J. Biol Chem, 1997, 272: 24046-24053).

Gilmore et al. do not teach the limitation of using an electrically enhancer element selected from the ANF 5' non-coding region. However, at the time the invention was made, McDonough et al. did teach elements derived from the ANF 5' non-coding region driving the expression of the luciferase gene upon electrical stimulation (page 24047, Experimental Procedures). Thus, it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to replace the enhancer of Gilmour et al. with the enhancer of McDonough et al., with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to employ such a chimeric enhancer-promoter containing in conjunction with an electrical pulse generator for controlled delivery of genes, and would have been expected to have a reasonable expectation of success in making and use such as the combined composition because the enhancer element selected from the ANF 5' non-coding region is proven to promote gene expression as desired, upon electrical stimulation.

Thus, the claimed invention was prima facie obvious at the time the invention was made.

13. Claims 1 and 26 are rejected under 35 USC 103(a) as being unpatentable over Gilmour et al., as applied to claim 1, in view of Kaye et al. (Circ Res, 1996, 78: 217-224).

Gilmour et al. do not teach a coding sequence selected from the group recited in claim 26. However, at the time the invention was made, Kaye et al. did teach activation of constitutive nitric oxide synthase (NOS) in rat myocytes upon electrical stimulation (Abstract, page 219, bridging page220, column 1). Thus, it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to employ a genetically engineer a cell with a construct comprising the nicotinic acethylcholine receptor γ subunit promoter of Gilmour et al. linked to a cDNA encoding for NOS to modulate NOS expression upon electrical stimulation, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to employ such a chimeric construct in conjunction with an electrical pulse generator for controlled expression of NOS, since Kaye et al. teach that NOS participates in the regulation of contractile function of cardiac muscle via nitric oxide synthesis, which in turn mediates muscarinic cholinergic signaling in cardiac myocytes and specialized pacemaker tissue, and modifies contractile response to β-adrenergic stimulation (page 217 bridging page 218). One of ordinary skill in the art would have been expected to have a reasonable

expectation of success in making and use such as the combined composition because the nicotinic acethylcholine receptor γ subunit promoter of Gilmour et al. is proven to modulate gene expression as desired, upon electrical stimulation.

Thus, the claimed invention was prima facie obvious at the time the invention was made.

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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